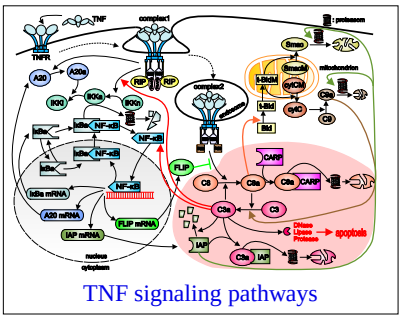
University of Stuttgart
Institute for Systems Theory and Automatic Control

# Analysing Biological Feedback with Tools from Control Theory

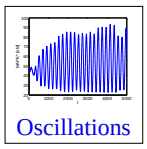
Steffen Waldherr, Thomas Eissing and Frank Allgöwer

## Background

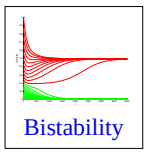
- Feedback circuits are used in biochemical networks to generate dynamical behavior like bistability and oscillations.
- Studying the influence of parameters on the dynamics of feedback circuits remains an important open problem.



TNF signaling pathways



Oscillations



Bistability

## Goals

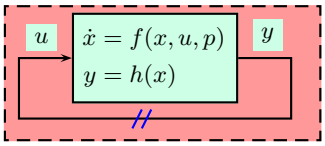
- Development of a systems theoretical approach to find **critical parameter values** responsible for a possible **qualitative change in dynamical behavior**.
- Implementation in a numerical method allowing to **search systematically for sustained oscillations** in high-dimensional parameter spaces.
- Evaluation of the influence of different feedback circuits on the dynamical behavior.

## Systems Theoretical Approach

- Dynamical system modeled with ODEs: state $x \in \mathbb{R}^n$
- Set of model parameters to be varied $p \in \mathbb{R}^m$

$$\dot{x} = F(x,p)$$

**Feedback loop representation** $\Longleftrightarrow$ **of dynamical system**



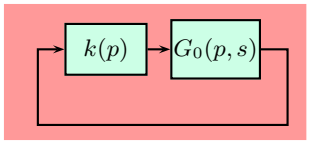

- **Loop breaking //** : open loop system, easier to analyse!
- Open loop linearisation, Laplace transformation: $G(p,s) = \frac{k(p)q(p,s)}{r(p,s)}$
- Condition for critical parameters, using concept of critical frequency and critical gain: $\frac{k_c q(p,j\omega_c)}{r(p,j\omega_c)} = 1$
  $\hookrightarrow$ closed loop eigenvalues on imaginary axis
  $\hookrightarrow$ change of dynamical properties

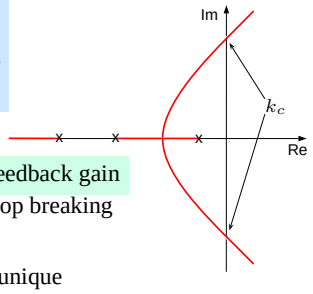
Benefit: **Closed loop properties** (i.e. stability or oscillations) deducible from **open loop analysis**.

## Determination of Critical Parameters

**Method:**

- Based on Nyquist criterion and concept of gain margin
- Numerical approach to determine parameter values for which closed loop eigenvalues cross the imaginary axis
- Implemented in MATLAB using a nonlinear optimization algorithm




**Advantages:**

- Parameters are lumped together in feedback gain
- Can use biological insight to place loop breaking

**Open problems:**

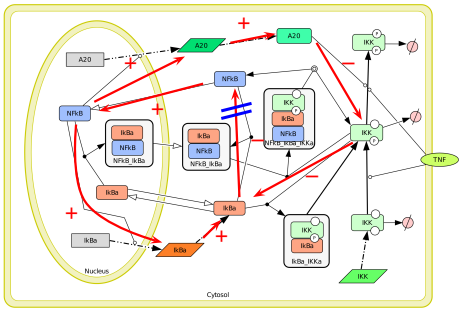
- Resulting critical parameters are not unique
- No guarantee for non-existence of critical parameters is obtained

## Application to NFκB Signaling

ODE model for the NFκB network:

- Model from Lipniacki *et. al.* (2004)
- Using mass action kinetics
- 14 molecular species
- 25 reaction parameters
- Multiple feedback circuits

- With a reduced (three-variable) model, Krishna *et. al.* (PNAS 2006) found sustained, spiky oscillations in NFκB.
- **Question:** Does the more detailed model allow for the **same qualitative behavior?**




**Loop breaking point //** at IκBα binding

Main parameter changes that were suggested by the developed search method:

- IκBα degradation increased by factor 7 (5);
- A20 transcript turnover increased by factor 3;
- IKKa turnover increased by factor 3;
- IκBα nuclear export increased by factor 3.7.

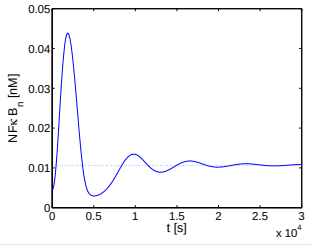
**Result:** Application of the developed method shows that spiky oscillations are possible in the Lipniacki model for physiological parameters.

**Next steps:**

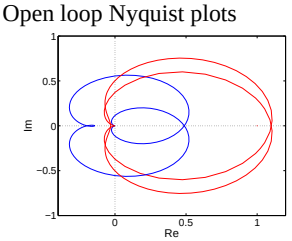
- Implication of different loop breaking points?
- Importance of individual parameters?
- Robustness of sustained oscillations?

Model behavior, reference parameters:

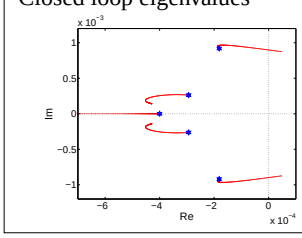
- stable equilibrium point
- damped oscillations




Open loop Nyquist plots



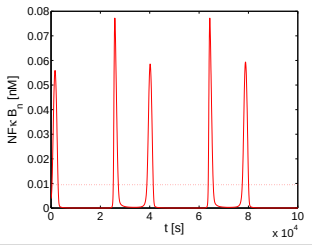

Closed loop eigenvalues




Varying parameters from reference to newly found values

Model behavior, new parameters:

- unstable equilibrium point
- sustained, spiky oscillations
- two spikes per period of approx. 6 h




## Conclusions

- New method to search for sustained oscillations in high-dimensional parameter space
- Method is **applicable to reasonably complex models**
- Application to NFκB model shows significance of results for biological questions.

**Contact:**
Steffen Waldherr, University of Stuttgart
Institute for Systems Theory and Automatic Control
Web: www.ist.uni-stuttgart.de/~waldherr/
Email: waldherr@ist.uni-stuttgart.de